CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

California Institute for Regenerative Medicine
Strategic Planning Advisory Committee
May 29, 2006

The second meeting of the Strategic Planning Advisory Committee (SPAC) included a summary of themes from the May 25th conference on Funding Stuctures, a presentation related to funding models for commercial entities as well as a discussion centered on the derivation of new ESC lines. In the course of this meeting, a number of ideas arose which are summarized below. This summary is intended to be comprehensive with respect to reporting these ideas; inclusion in this list does not imply any commitment or endorsement by the CIRM.

A. Themes from May 25 Scientific Conference on Funding Mechanisms and SPAC Comments

1. Partnerships can advance research aims.
   a. CIRM can push progress faster and further and leverage its own research through partnerships with other groups.
   b. The CIRM should look to partner with other agencies. The Juvenile Diabetes Research Foundation (JDRF), for example, partners with many organizations in many countries.
   c. CIRM needs to look for ways to not be hampered in these partnerships by its inability to use CIRM funds out of state.
   d. CIRM should look to partner with groups that fill needs and gaps. For example, CIRM could partner with an existing clinical trial network.
   e. CIRM should make an effort to set up a mechanism where, if approached for a partnership, it can accommodate it.
   f. CIRM should start thinking about how industry should be involved in this initiative.

2. Granting agencies can play an active role in shaping grants.
   a. Some organizations, such as High Q Foundation (High Q) and the National Institute of Standards and Technology (NIST) play an active role in shaping the grants they received and actively managed their programs.

3. Disease focused research is an option but not a necessity.
   a. Some organizations, namely High Q, JDRF, and Cure Autism Now (CAN) target funding to the specific disease that is their mission focus.

b. Some organizations have broader initiatives. The Canadian Stem Cell Network started with a disease-focused approach, but switched away from this model. Now it funds broad, enabling technologies with the belief that the research it funds should be applicable to a number of other diseases.

4. The importance of early phase discovery research can not be overemphasized.
   a. CIRM should pursue high quality science. The only restraint placed on funding is that it should support world-class science. Don't create boundaries on the science.
   b. Because the federal government is not funding certain types of research, CIRM should look to fill that gap.
   c. CIRM must be aware that it will be difficult to put out large numbers of grants without potentially exhausting their review committee. For example, JDRF funds about $120M in research per year to about 500 investigators, has about 15 different types of grants, and used 150 scientific reviewers last year. That is far more reviewers than CIRM has.
   d. CIRM should consider having workshops like the ones conducted by High Q where expert participants help shape the nature of the initiative.
      i. In an effort to maximize the speed of therapy development, the workshops conducted by High Q bring together leading scientists to focus on evaluating the best critical path to develop those therapies or to find related enabling technologies.
      ii. Some of these workshops also include a review of proposals with an eye toward whether or not they fit into the critical path discussed above.

B. Presentation on Funding Mechanisms from the Private Sector by Dr. Mary Maxon (Slide presentation is available online on the CIRM website)

1. Overview of slide presentation
   a. There are four stages of innovation
      i. Basic research
      ii. Applied research
      iii. Development
      iv. Commercialization
   b. Innovation is neither linear nor unidirectional. A large part of science is failure, this helps inform further research. Overall success rate for clinical development is about 10% Even when trials fail, information derived from the failures can inform future development
   c. The therapy development timeline has a number of "go" / "no-go" decision points. It takes time to get therapies to market and costs escalate exponentially with progression along the timeline.
   d. Academia is centered around basic research; companies may also conduct basic research but are typically known more for their expertise in applied research and clinical development. Also, major medical schools and academic medical centers play a huge role in clinical development as they are the sites where academic and company-sponsored clinical research is conducted.

e. Key questions were proposed regarding CIRM funding for the commercial sector including:
    i. The amount and types of funding for companies
    ii. The type of review process to be used for companies
    iii. The target for company funding (e.g. gap funding for early stage translational companies and / or funding support for clinical development.)
    iv. whether funding for the corporate sector should be "back-end loaded" to support development of promising therapies
f. Federal funding models for the commercial sector include:
    i. SBIR (Small Business Innovation Research)
    ii. ATP (Advanced Technology Program)
        – These two programs work on the belief that technology development is inherently valuable and provide early stage financial support for high-risk technologies.
        – The SBIR budget is a set aside of 2.5% annually, about $2B per year across 50 programs, 30-40% of which are health-care related. The ATP budget is smaller, having distributed about $2.1B over 14 years.
        – ATP targets a failure rate of 50% to ensure innovation. It focuses on whether:
            + projects are scientifically feasible based on evidence
            + projects have high spillover potential
            + a path to commercialization exists
            + funding for this idea is unlikely - letters of rejection from venture capital companies are encouraged
g. State models include:
    i. Maryland - TEDCO (Technology Development Corporation)
    ii. Pennsylvania - Ben Franklin Technology Partners
    iii. California - UC Discovery Grants
h. Foundation models often:
    i. Have both strategic and 'response mode" programs that are outcome focused and include active management by the foundation.
    ii. Recognize company's likely need to require or attract additional investment to realize potential of the research.
    iii. Provide a range of funding options that can include collaborations with academia.
i. Differences in foundation funding:
    i. Structure for funding commercial sector
        – The Wellcome Trust Fund spun off its commercial funding arm but then brought back in house.
        – Cystic Fibrosis spun out a commercial funding arm just recently
    ii. There is no universal expectation of repayment of funds (so expect payment, some don't).

j. The common thread among all types of funding is a recognition that the commercial sector offers means to develop and commercialize research results for public benefit.

C. Discussion Following Presentations on Funding Mechanisms

1. The public records requirements may be a cause of substantial concern to commercial firms receiving grants in that they will have disclosed proprietary information in the grant application.
   a. NIST has been able to handle this issue because, by statute, it is not allowed to disclose any details of the grants it receives or funds.
   b. NIH, upon a FIA request, allows the awardee to redact confidential information from a document before making it available

2. Does CIRM have a role in helping to develop small companies?
   a. The wording of Proposition 71 is set up to fund the best science.
   b. Small companies should have to compete with academic centers in the usual review process.
   c. CIRM should also consider talking to venture capitalists to better understand that funding model.

D. Discussion - New ESC Lines: Focus for Early Funding? (Please refer to outline available on CIRM website)

1. Availability of Stem Cell Lines
   a. Although there are a number of reported derived lines, their availability varies.
   b. New lines may need to be derived if only to replace existing lines lost to contamination or genetic / phenotypic drift.
   c. Some participants felt that CIRM should make a considerable effort to develop and distribute lines and establish common standards.
      i. However, other felts that it may be premature to engage in a large effort to derive large numbers of ESC lines absent a specific research purpose or without standardization in place.
      ii. CIRM may wish to consider sponsoring a workshop that will help standardize the way ESC lines are developed
   d. CIRM should be aware of commercial barriers and national policy concerns that need to be overcome for the distribution of international and commercial lines.
   e. The derivation of ESC lines is not difficult, but expertise is critical. Gaining the expertise to derive lines involves a lot of learning and trial and error.
   f. There is an interest in deriving lines with genetic defects.
   g. One estimate is that at least 150 “normal” stem cell lines should be available to accommodate the genetic diversity based on a study of a (UK) population.
      Note: Please see Civin, C.I., Rao, M. "How many ESC lines are sufficient? A U.S. Perspective", Stem Cell 24:800-803, 2006 that covers many of the issues discussed today.

2. There are several views on whether establishing GMP ESC lines should be a priority for CIRM in the early years.

a. GMP or Good Manufacturing Practices when applied to cell line derivation and maintenance means rigorous attention to and documentation of all the materials and procedures used in the deriviation, selection, and maintenance of a cell line as well as characterization of the cell line so as to have reasonable understanding of its identity and stability. GMP lines are not necessary for research purposes but are required if used in humans.
b. One school of thought holds that if GMP lines are available early on, then there will not be a need to "backtrack" and develop such lines when the science gets to the stage where therapies are ready to be developed.
c. The other school of thought holds that there is a lot of basic research that still needs to be done so developing GMP lines at this point may be unnecessary. It may be premature to establish GMP lines as we are not close to clinical applications.

3. CIRM's role in funding new ESC lines
   a. A bill recently passed in the House (HR 810) that calls for expanding the number of ESC lines eligible for federal funding to on the order of 100. Assuming this bill becomes law, then federal funds will be available to derive new lines and the role of CIRM with regards to deriving new lines will need to be reevaluated.
      i. Even if the House Bill HR 810 passes, researchers may not be in a position to move quickly to derive new lines.
   b. There is still uncertain availability for the world-wide population of ESC lines.
   c. CIRM could still serve a large need by funding the derivation of new ESC lines. Given the flat state of NIH funding, funding will still be tight even if the bill passes. It is not necessarily innovative to derive new ESC lines so funding may be difficult to come by.
   d. CIRM might consider establishing core facilities in the state to derive and distribute ESC lines. Researchers will then not have to re-invent something that already exists and is working well. CIRM should make an effort to find out what is already available in order to best maximize its resources.

E. Moving From Preclinical to Clinical Stages and Role of CIRM

1. CIRM should look to target low-hanging fruit. Even if funds are disbursed now, it is possible that clinical trials will not start for another 10 years. A goal of CIRM should be to have at least some Phase I and Phase II clinical trials started at the end of 10 years.

2. ESC research could potentially improve cellular toxicity testing and reduce the number of drugs that fail in clinical trials.
   a. There are many different ways compounds fail toxicity tests; toxicity is difficult to generalize.

3. CIRM should not fund late stage clinical trials, but rather should facilitate the transfer of clinical development stage programs to the private sector through venture capitalists, licensing and other mechanisms. CIRM should focus on the earlier stage work where venture capitalists currently fear to tread

4. CIRM should be looking for opportunities that will generate continued funding after the mandate of Proposition 71 expires.

5. CIRM should consider funding translational clinical research

    a. Opportunities may exist to expand on existing (HSC) therapies
        i. Issues relating to immune tolerance remain a key factor limiting the use of this therapy to patients with limited options.
        ii. There is already an existing infrastructure for bone marrow transplants and much is known about this type therapy.
        iii. Clinical trials are being pursued in a broad array of conditions including hematopoietic and inflammatory diseases
        iv. This is a translational area that might get us to clinical trials sooner.

6. This topic will be further discussed at the July 13 conference for the ICOC and the public and in other meetings